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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,399	01/05/2006	Alan Berry	21841USWO(C038435/0196234	3243
7590	11/29/2006			EXAMINER RAGHU, GANAPATHIRAM
Stephen M Haracz Bryan Cave 1290 Avenue of the Americas New York, NY 10104			ART UNIT 1652	PAPER NUMBER

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/563,399	BERRY ET AL.
	Examiner Ganapathirama Raghu	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 05 January 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-7 and 9 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-7 and 9 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 01/05/06.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) Notice of Informal Patent Application
- 6) Other: _____

DETAILED ACTION

Claims 1-7 and 9 are pending are pending in this application and are now under consideration for examination.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). This application is a 371 PCT/EP04/07025 filed on 06/29/2004 and claims the priority date of EPO application 03015367.0 filed on 07/08/2003.

Abstract

The abstract of the disclosure is objected to because the abstract should be on a separate sheet of paper. Correction is required. See MPEP § 608.01(b).

Drawings

Drawings submitted on 01/05/2006 along with the application are accepted for examination purposes only.

Claim Objections

Claims 1 and 9 are objected to because of the following informalities:

Applicant is advised that should claim 1 be found allowable, claim 9 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight

difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 1, 2, 4 and 9 are objected to, due to the following informality: Claims 1, 2, 4 and 9 uses abbreviation CoQ10 in the claims. Examiner suggests expanding the abbreviation to recite the full form of what the abbreviation stands for at least in the first recitation of the abbreviation. Appropriate correction is required.

Claim Rejections 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7 and 9 are directed to a process for CoQ10 production comprising introducing a mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter* and said modified microorganism. Claims 1-7 and 9 are rejected under this section 35 U.S.C. 112, because the claims are directed to a process for CoQ10 production by a modified bacterium of genus *Rhodobacter*, wherein the bacterium has been modified by introducing a mevalonate operon from a microorganism belonging to the

genus of *Paracoccus* and as said modified bacterium of genus *Rhodobacter* involves a genus of polynucleotides of mevalonate operon genes isolated from a microorganism belonging to the genus *Paracoccus* with no support in the specification for the structural details associated with the function i.e., mevalonate operon activity, encoding polynucleotide isolated from genus *Paracoccus*. No description of identifying characteristics of all of the sequences of an isolated polynucleotide having mevalonate operon activity from the genus *Paracoccus* and the use of said polynucleotides in a modified CoQ10 producing bacterium of genus *Rhodobacter* has been provided by the applicants in the specification. No information, beyond the characterization of a plasmid pBR-K-mev-op-R114 (plasmid containing the first 4 genes of the mevalonate operon as described in detail in Example: 6 of WO 02/0999095 and isolated by PCR amplification by using PCR primer *hcs*-5326 with SEQ ID NO: 1 and a PCR primer *mvd*-9000 with SEQ ID NO: 2 that flanks SEQ ID NOs : 46 to 52 of WO 02/099095, having a mutation in *mvk* gene, resulting in a change of amino acid residue 265 from alanine to valine; A265V as compared to the wild-type mevalonate operon sequence of *Paracoccus zeaxanthinifaciens* strain ATCC 21588, pages 8-9 of Specification) has been provided by the applicants, which would indicate that they had possession of the claimed genus of all of the sequences of an isolated polynucleotide having mevalonate operon activity from the genus *Paracoccus* and the use of said polynucleotides in a modified CoQ10 producing bacterium of genus *Rhodobacter*. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for CoQ10 production comprising introducing a plasmid pBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens* of strain ATCC 21588 into a microorganism belonging to the *Rhodobacter sphaeroides* and said modified microorganism, does not reasonably provide enablement for a process for CoQ10 production comprising introducing any mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter* and said modified microorganism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claim.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-7 and 9 are so broad as to encompass a process for CoQ10 production comprising introducing any mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter* and said modified microorganism. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of bacteria broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its

structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. A skilled artisan must have detailed knowledge with regard to how the protein/gene to be enhanced is regulated within said cell and be provided with detailed knowledge with regard to how modifications of said regulatory systems will effect the desired gene and other genes of the bacteria. However, in this case the disclosure is limited to process for CoQ10 production comprising introducing a plasmid pBR-K-mev-op-R114 (plasmid containing the first 4 genes of the mevalonate operon as described in detail in Example 6 of WO 02/0999095 and isolated by PCR amplification by using PCR primer *hcs*-5326 with SEQ ID NO: 1 and a PCR primer *mvd*-9000 with SEQ ID NO: 2 that flanks SEQ ID NOs : 46 to 52 of WO 02/099095, having a mutation in *mvk* gene, resulting in a change of amino acid residue 265 from alanine to valine; A265V as compared to the wild-type mevalonate operon sequence) comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens* of strain ATCC 21588 into a microorganism belonging to the *Rhodobacter sphaeroides* and said modified microorganism. In view of the great breadth of the claims, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a encoded polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue

experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims for a process for CoQ10 production comprising introducing any mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter* and said modified microorganism, because the specification does not establish: (A) regions of the protein/polynucleotide structure which may be modified to produce the desired effect of the encoded mevalonate operon activity wherein the polynucleotides are from any member of genus *Paracoccus* or strains (B) the general tolerance of the polypeptide and the polynucleotide encoding mevalonate operon activity to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a process for CoQ10 production comprising introducing any mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter* and said modified microorganism. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polynucleotides and encoding polypeptides of mevalonate operon activity having the desired biological characteristics in a process for CoQ10 production comprising introducing any mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter* and isolation of said modified microorganism is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections: 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berry et al., (WO 02/099095 A2, publication date 12/121/2002; In IDS), Hahn et al., (WO 02/10398 A2, date of publication, 02/07/23002; In IDS), Gokarn et al., (US PGPUB : US 2003/0219798 A1, date of publication 11/07/ 2003 claiming priority to US Application No.: 10/381,779 and PCT/US01/30328 filed on 09/28/2001), and Yoshida et al., (J. Gen. Appl. Microbiol., 1998, Vol. 44: 19-26; In IDS). Claims 1-7 and 9 are directed to a process for CoQ10 production comprising introducing a mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter* and said modified microorganism.

The reference of Berry et al., (*supra*) disclose the sequence of plasmid pBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens* of strain ATCC 21588 (plasmid containing the first 4 genes of the mevalonate operon as described in detail in Example 6 of WO 02/099095 and isolated by PCR amplification by using PCR primer *hcs-5326* with SEQ ID NO: 1 and a PCR primer *mvd-9000* with SEQ ID NO: 2 that flanks SEQ ID NOs : 46 to 52 of WO 02/099095, having a mutation in *mvk* gene, resulting in a change of amino acid residue 265 from alanine to valine; A265V as compared to the wild-type mevalonate operon sequence).

Hahn et al., et al., (*supra*) disclose the methods of manipulation of the mevalonate and isoprenoid pathways to create novel traits in organisms of interest for the production of isoprenoids (CoQ10).

Gokarn et al., (*supra*) disclose the identification of polynucleotide sequences involved in the isoprenoid production and also use of *Rhodobacter sp.*, microorganism for the production of CoQ10 by introducing heterologous genes involved in the isoprenoid production (CoQ10) in said microorganism (Paragraphs 0028-0033, 0137-0147 and 0157-0163 and claims 75-102).

Yoshida et al., (*supra*) disclose that *Rhodobacter sphaeroides* as an excellent producer and host for the production of ubiquinone-10 (CoQ10) an isoprenoid compound (Abstract and Introduction section, page 19).

The main objective of the instant application relates to a method for the production of Coenzyme Q-10 (CoQ10) by microorganisms. More particularly, the present invention relates to a method for increased production of Coenzyme Q-10 by transformed microorganisms and the transformants themselves. The transformants are microorganisms of the genus *Rhodobacter*, preferably of the species *R. sphaeroides* which have been transformed with the mevalonate operon from a different microorganisms.

The teachings of Berry et al., et al., (*supra*) disclose the sequence of plasmid pBR-K-mev-op-R114, comprising a mevalonate operon of *Paracoccus zeaxanthinifaciens* strain ATCC 21588, the source of the genomic DNA of the instant application and the methods for plasmid construction and use of the same for transforming microorganism of interest. Similarly, the teachings of Hahn et al., also disclose the methods of manipulation of the mevalonate and isoprenoid pathways to create novel traits in organisms of interest for the production of

isoprenoids (CoQ10) and further, the teachings of Gokarn et al., and Yoshida et al., (*supra*) disclose the advantages in the use of *Rhodobacter sp.*, microorganism for the production of CoQ10 by introducing heterologous genes involved in the isoprenoid production (CoQ10).

The above mentioned references teach all the elements of the instant application and combining the teachings of the above references it would have been obvious to one of ordinary skill in the art at the time of the instant invention to generate a bacterium that can be used for a process in the production CoQ10 and such a bacterium and said process would comprise introducing a mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter*. One of ordinary skill in the art would have been motivated to make a CoQ10 producing bacterium of the genus *Rhodobacter* because of the advantages as exemplified in the references of Gokarn et al., and Yoshida et al.,. One of ordinary skill in the art would have had a reasonable expectation of success as all of the above-cited references teach all the elements to a method for the production of Coenzyme Q-10 (CoQ10) by microorganisms.

Therefore, the above references render claims 1-7 and 9 *prima facie* obvious to one of ordinary skill in the art.

Conclusion

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on 8 am - 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or

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proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ganapathirama Raghu, Ph.D.

Patent Examiner

Art Unit 1652

Nov. 01, 2006.

Rebecca E. Prouty
REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600
1600